

CLAIMS

What is claimed is:

1. A method for increasing mitochondrial respiration comprising administering a compound
5 having a slope calculated from the equation

$$X^n = (Y_2 - Y_0) / (Y_1 - Y_0)$$

wherein

Y_0 is the degree of stimulation measured as counts per minute (cpm) in Assay (I) in control samples without added test compound,

10 and

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/2$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $2 \times EC_{50}$, and

15

X is 2,

or

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/3$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $3 \times EC_{50}$, and

20

X is 3,

and

n is the slope,

of a value less than the value for the slope calculated from the above equation with carbonyl-
cyanide *p*-trifluoromethoxy-phenylhydrazone as test compound in Assay (I), or a pharmaceu-
25 tically acceptable salt, solvate or prodrug thereof.

2. A method for treating a disorder, disease or condition benefiting from an increase in mitochondrial respiration in a patient in need thereof comprising administering a therapeutically
30 effective amount of a compound having a slope calculated from the equation

$$X^n = (Y_2 - Y_0) / (Y_1 - Y_0)$$

wherein

Y_0 is the degree of stimulation measured as counts per minute (cpm) in Assay (I) in control samples without added test compound,

35

and

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/2$,

5 Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $2 \times EC_{50}$, and

X is 2,

or

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/3$,

10 Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $3 \times EC_{50}$, and

X is 3,

and

n is the slope,

15 of a value less than the value for the slope calculated from the above equation with carbonyl-cyanide *p*-trifluoromethoxy-phenylhydrazone as test compound in Assay (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof.

20 3. A pharmaceutical composition for treating a disorder, disease or condition benefiting from an increase in mitochondrial respiration in a patient in need thereof comprising a compound having a slope calculated from the equation

$$X^n = (Y_2 - Y_0) / (Y_1 - Y_0) = X^n$$

wherein

25 Y_0 is the degree of stimulation measured as counts per minute (cpm) in Assay (I) in control samples without added test compound,

and

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/2$,

30 Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $2 \times EC_{50}$, and

X is 2,

or

35 Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/3$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $3 \times EC_{50}$, and

X is 3,

and

5 n is the slope,

of a value less than the value for the slope calculated from the above equation with carbonyl-cyanide *p*-trifluoromethoxy-phenylhydrazine as test compound in Assay (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof.

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4. A method according to claim 2 wherein the disorder, disease or condition is selected from obesity, atherosclerosis, hypertension, diabetes, type 2 diabetes, impaired glucose tolerance, dyslipidemia, coronary heart disease, gallbladder disease, osteoarthritis, cancer, endometrial cancer, breast cancer, prostate cancer, colon cancer, or the maintenance of a weight loss.

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5. A method according to claim 4, wherein the condition is obesity.

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6. A method according to claim 4, wherein the disease is type 2 diabetes.

7. A method according to claim 6, wherein the patient in need thereof is obese.

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8. A method according to claim 4, wherein the disease is dyslipidemia.

9. A method according to claim 8, wherein the patient in need thereof is obese.

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10. A method for reducing reactive oxygen species comprising administering a compound having a slope calculated from the equation

$$X^n = (Y_2 - Y_0) / (Y_1 - Y_0) = X^n$$

35 wherein

Y_0 is the degree of stimulation measured as counts per minute (cpm) in Assay (I) in control samples without added test compound,

and

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/2$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $2 \times EC_{50}$, and

X is 2,

or

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/3$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $3 \times EC_{50}$, and

X is 3,

and

n is the slope,

of a value less than the value for the slope calculated from the above equation with carbonyl-cyanide *p*-trifluoromethoxy-phenylhydrazone as test compound in Assay (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof.

11. A method for treating a disorder, disease or condition benefiting from a reduction of reactive oxygen species in a patient in need thereof comprising administering a therapeutically effective amount of a compound having a slope calculated from the equation

$$X^n = (Y_2 - Y_0) / (Y_1 - Y_0)$$

wherein

Y_0 is the degree of stimulation measured as counts per minute (cpm) in Assay (I) in control samples without added test compound,

and

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/2$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $2 \times EC_{50}$, and

X is 2,

or

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/3$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $3 \times EC_{50}$, and

5 X is 3,

and

n is the slope,

of a value less than the value for the slope calculated from the above equation with carbonyl-
cyanide *p*-trifluoromethoxy-phenylhydrazone as test compound in Assay (I), or a pharmaceu-
10 tically acceptable salt, solvate or prodrug thereof.

12. A pharmaceutical composition for treating a disorder, disease or condition benefiting from
a reduction of reactive oxygen species in a patient in need thereof comprising a compound
15 having a slope calculated from the equation

$$X^n = (Y_2 - Y_0) / (Y_1 - Y_0)$$

wherein

Y_0 is the degree of stimulation measured as counts per minute (cpm) in Assay (I) in
control samples without added test compound,

20 and

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/2$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $2 \times EC_{50}$, and

25 X is 2,

or

Y_1 is the degree of stimulation measured as cpm in Assay (I) with added test compound in a concentration of $EC_{50}/3$,

Y_2 is the degree of stimulation measured as cpm in Assay (I) with added test compound in concentration of $3 \times EC_{50}$, and

30

X is 3,

and

n is the slope,

of a value less than the value for the slope calculated from the above equation with carbonyl-cyanide *p*-trifluoromethoxy-phenylhydrazone as test compound in Assay (I), or a pharmaceutically acceptable salt, solvate or prodrug thereof.

5

13. A method according to claim 11, wherein the disorder, disease or condition to be treated is selected from the aging process, damage of heart tissue, damage of endothelial cells, damage of neuronal tissue, Alzheimer's disease, cancer, cataract, diabetic microvascular diseases in the retina, renal glomerus and peripheral nerve cell apoptosis.

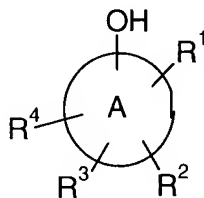
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14. A method according to claim 1, wherein the compound is a chemical uncoupler as defined in Assay (II), as described in the specification.

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15. A method according to claim 1, wherein the compound is a cation.

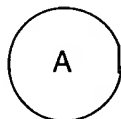
16. A method according to claim 1, wherein the compound is of the general formula (I)



(I)

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wherein



is an aryl, or heteroaryl,

25 R^1 is halogen, $-\text{CHO}$, $-\text{CO}_2R^{32}$, $-\text{COR}^{32}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{33}$, $-\text{C}(\text{R}^{33})(\text{R}^{34})$, $-\text{SOR}^{32}$, $-\text{SO}_2R^{32}$ or aryl substituted with from one to five substituents selected from halogen, $-\text{CHO}$, $-\text{CO}_2R^{32}$, $-\text{COR}^{32}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{33}$, $-\text{CH}(\text{R}^{33})(\text{R}^{34})$, $-\text{SOR}^{32}$, $-\text{SO}_2R^{32}$, wherein

R^{32} is hydrogen, alkyl, aryl, or heteroaryl; and

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R^{33} and R^{34} independently of each other are halogen, $-\text{CHO}$, $-\text{CO}_2R^{35}$, $-\text{COR}^{35}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SOR}^{35}$, $-\text{SO}_2R^{35}$, wherein

R^{35} is hydrogen or alkyl;

and is attached on a carbon atom adjacent to the carbon atom to which the hydroxy group is attached;

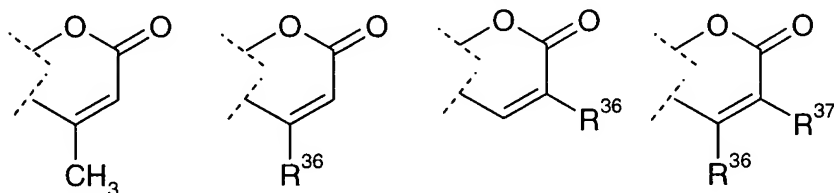
R^2 is $\text{C}(\text{X})_3$, NO_2 , alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl, wherein

X is halogen; and

R^3 and R^4 independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

or

R^2 and R^3 together forms one of the diradicals



wherein

R^{36} and R^{37} , independently of each other, are hydrogen, halogen, $\text{C}(\text{X})_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl, wherein

X is halogen;

and where the two connecting atoms are connected to adjacent carbon atoms; and

R^4 is hydrogen, halogen, $\text{C}(\text{X})_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl,

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

17. a method according to claim 16, wherein the compound is selected from

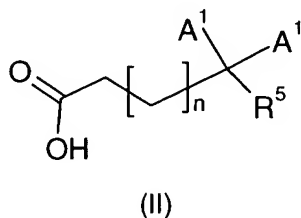
4-methoxy-2-nitrophenol,

4-hydroxy-3-nitroacetophenone, or

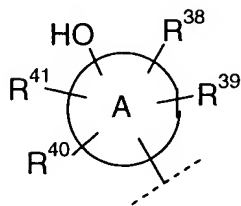
7-hydroxy-4-methyl-8-nitro-chromen-2-one.

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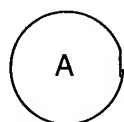
18. A method according to claim 1, where the compound is of the general formula (II)



wherein A¹ is



, wherein



is an aryl, or heteroaryl,

R³⁸ is halogen, -CHO, -CO₂R⁴², -COR⁴², -SO₃H, -CCl₃, -CF₃, -NO, -NO₂, -CN, -SOR⁴², or -SO₂R⁴², wherein

R⁴² is hydrogen or alkyl;

and is attached to a carbon atom adjacent to the carbon atom to which the hydroxy group is attached;

R³⁹, R⁴⁰, and R⁴¹ independently of each other are hydrogen, alkyl, nitro, cyano, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

15 R⁵ is hydrogen or alkyl; and

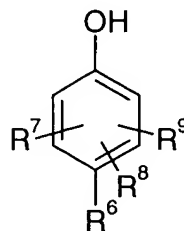
n is an integer of from 0 to 10

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

20 19. A method according to claim 18 wherein the compound is 4,4-bis-(4-hydroxy-3-nitrophenyl)-valeric acid.

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20. A method according to claim 1 wherein the compound is of the general formula (III)



(III)

wherein

- 5 R^6 is halogen, $-\text{CHO}$, $-\text{CO}_2R^{43}$, $-\text{COR}^{43}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{44}$, $-\text{C}(R^{44})(R^{45})$, $-\text{SOR}^{43}$, $-\text{SO}_2R^{43}$ or aryl substituted with from one to five substituents selected from halogen, $-\text{CHO}$, $-\text{CO}_2R^{43}$, $-\text{COR}^{43}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{44}$, $-\text{CH}(R^{44})(R^{45})$, $-\text{SOR}^{43}$, $-\text{SO}_2R^{43}$, wherein

R^{43} is hydrogen or alkyl; and

- 10 R^{44} and R^{45} independently of each other are halogen, $-\text{CHO}$, $-\text{CO}_2R^{46}$, $-\text{COR}^{46}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SOR}^{46}$, $-\text{SO}_2R^{46}$, wherein

R^{46} is hydrogen, alkyl, or aryl;

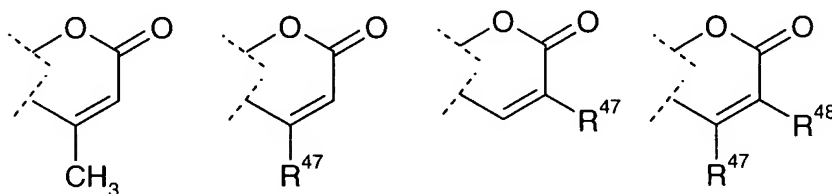
R^7 is alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-; and

R^8 and R^9 independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-

- 15 C(O)-, alkyl-C(O)-O-, or aryl;

or

R^7 and R^8 together forms the diradical



- wherein R^{47} and R^{48} , independently of each other, are hydrogen, alkyl, nitro, halogen,
20 alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-,

where the two valence atoms are connected to adjacent carbon atoms; and

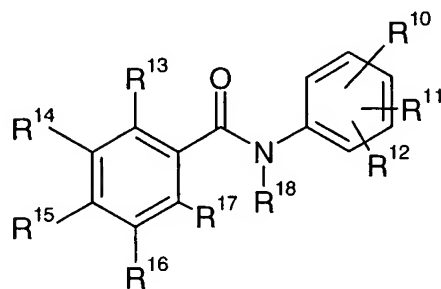
R^9 is hydrogen, alkyl, nitro, halogen, alkyl-O-, or alkyl-C(O)-

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

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21. A method according to claim 1, wherein the compound is of the general formula (IV)



(IV)

wherein

5 R¹⁰, R¹¹ and R¹² independently of each other are hydrogen, trifluoromethyl, nitro, cyano, alkyl-S-, R⁴⁹SO_y-, R⁴⁹-O-, N(R⁵⁰)(R⁵¹)-, alkyl, halogen, or aryl-S-, wherein y is an integer of 1 or 2;

 R⁴⁹, R⁵⁰ and R⁵¹ independently of each other are hydrogen or alkyl;

 wherein at least one of R¹⁰, R¹¹ and R¹² is different from hydrogen;

10 and

 R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ independently of each other are hydrogen, halogen, hydroxy, cyano, or alkyl, aryl, aryl-S-, or heteroaryl, optionally substituted with halogen;

 or

15 R¹³ and R¹⁴ together form a conjugated alkenylene, which together with the benzene ring forms a fused aromatic ring system, which may optionally be substituted with one or more substituents selected from the group consisting of hydroxy, methyl, halogen, CF₃, alkyl-O-, nitro, and cyano;

 and

20 R¹⁵, R¹⁶ and R¹⁷, independently of each other, are hydrogen, halogen, hydroxy, halogen, or alkyl optionally substituted with halogen

 or

25 R¹⁴ and R¹⁵ together form a conjugated alkenylene, which together with the benzene ring forms a fused aromatic ring system, which may optionally be substituted with one or more substituents selected from the group consisting of hydroxy, methyl, halogen, CF₃, alkyl-O-, nitro, and cyano;

 and

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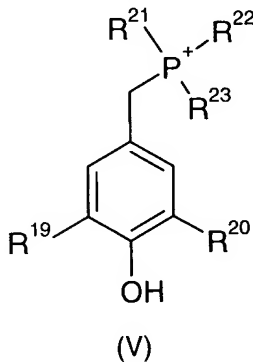
R^{13} , R^{16} and R^{17} independently of each other are hydrogen, halogen, hydroxy, halogen, or alkyl, aryl or heteroaryl, optionally substituted with halogen;

and

- 5 R^{18} is hydrogen;
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

22. A method according to claim 21, wherein the compound is selected from
10 tert-butyl-5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxy-6-methylbenzamide,
N-1-[4-cyano-3-(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)benzamide,
N-(4-cyanophenyl)benzamide,
2'-chloro-1-hydroxy-4'-nitro-2-naphthanilide,
N-(2-chloro-4-bromophenyl)-5-bromosalicylanilide,
15 N-(2-chloro-4-nitrophenyl)-3-tert-butyl-6-methylsalicylanilide,
3,6-dinitrocarbazole, or
N-(3-cyano-4-phenylsulfanyl-phenyl)-3-trifluoromethyl-benzamide.

- 20 23. A method according to claim 1, wherein the compound is of the general formula (V)



wherein R^{19} and R^{20} independently of each other are alkyl;

and

- 25 R^{21} , R^{22} and R^{23} independently of each other are selected from alkyl, cycloalkyl, or aryl
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

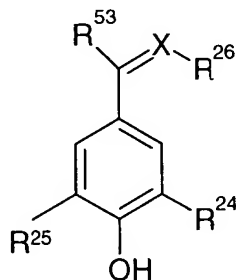
24. A method according to claim 23, wherein the compound is selected from

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(3,5-di-tert-butyl-4-hydroxybenzyl)triphenylphosphonium bromide,
 (3,5-di-tert-butyl-4-hydroxybenzyl)tricyclohexylphosphonium bromide,
 (3,5-di-tert-butyl-4-hydroxybenzyl)tributylphosphonium bromide, or
 (3,5-di-tert-butyl-4-hydroxybenzyl)trioctylphosphonium bromide.

5

25. A method according to claim 1, wherein the compound is of the general formula (VI)



(VI)

10

wherein

R^{24} and R^{25} independently of each other are alkyl or cycloalkyl;

and

X is $=C(R^{52})-$; wherein

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R^{52} is hydrogen, cyano, nitro, alkyl- $S(O)_2-$, tetrazole, alkyl-S-, alkyl-C(O)-, or alkyl-O-C(O)-, halogen, haloalkyl, $(R^{53})_2-N-C(O)-$, $-P(O)(O-R^{53})_2$, aryl, heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents selected from nitro, cyano, halogen, haloalkyl, -C(O)- R^{53} , -C(O)-O- R^{53} , -C(O)-N- $(R^{53})_2$, - $S(O)_2$ -O- R^{53} , -S(O)- R^{53} , - $S(O)_2$ - R^{53} , - $S(O)_2$ -N- $(R^{53})_2$, or -O- R^{53} , wherein

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R^{53} is hydrogen, or alkyl or phenyl optionally substituted with halogen; and

R^{26} is cyano, nitro, R^{54} - $S(O)_2-$, tetrazole, alkyl-C(O)-, or alkyl-O-C(O)-, haloalkyl, -S(O)-alkyl, - $S(O)_2$ O-alkyl, - $S(O)_2$ -N- $(R^{54})_2$, -C(O)-N- $(R^{54})_2$, wherein

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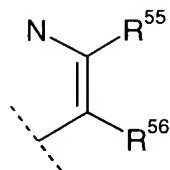
R^{54} is hydrogen, or alkyl or phenyl optionally substituted with halogen;

or

X is =N-, and

R^{26} is cyano, nitro, R^{54} - $S(O)_2-$, alkyl-C(O)-, alkyl-O-C(O)-, or

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wherein

R^{54} is hydrogen, or alkyl or phenyl optionally substituted with halogen; and
 R^{55} and R^{56} independently of each other are cyano, nitro, R^{57} -S(O)₂-, al-
 5 kyl-C(O)-, or alkyl-O-C(O)-, wherein

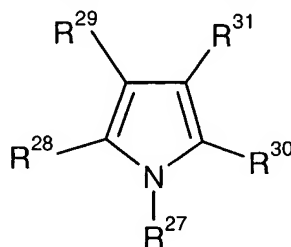
R^{57} is hydrogen, or alkyl or phenyl optionally substituted with halo-
 gen;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

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26. a method according to claim 25, wherein the compound is selected from
 2-cyano-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-acrylic acid ethyl ester,
 2-(3,5-di-tert-butyl-4-hydroxy-benzylidene)-malonic acid diethyl ester,
 2-amino-S-[(3,5-di-tert-butyl-4-hydroxybenzylidone)-amino]-but-2-enedinitrile, or
 15 2-(3,5-di-tert-butyl-4-hydroxy-benzylidene)-indan-1,3-dione.

27. A method according to claim 1, wherein the compound is of the general formula (VII)



(VII)

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wherein

R^{27} is hydrogen or alkyl-O-CH₂-;

R^{28} and R^{29} independently of each other are hydrogen, halogen, dicyanovinyl,
 cyano, nitro, dinitrovinyl, alkyl optionally substituted with halogen, or aryl optionally
 25 substituted with one or more substituents selected from the group consisting of
 halogen, dicyanovinyl, cyano, nitro, and dinitrovinyl,

or

R^{28} and R^{29} together forms a benzene ring optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} -alkyl, dicyanovinyl, cyano, nitro, and dinitrovinyl;

and

5 R^{30} is halogen, dicyanovinyl, cyano, nitro, dinitrovinyl, alkyl optionally substituted with halogen, or aryl optionally substituted with one or more substituents selected from the group consisting of halogen, dicyanovinyl, cyano, nitro, and dinitrovinyl; and R^{31} is hydrogen, halogen, dicyanovinyl, cyano, nitro, dinitrovinyl, alkyl optionally substituted with halogen, or aryl optionally substituted with one or more substituents
10 selected from the group consisting of halogen, dicyanovinyl, cyano, nitro, and dinitrovinyl;

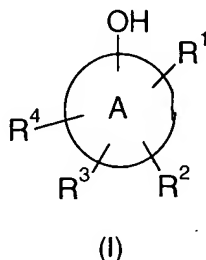
or

R^{30} and R^{31} together forms a benzene ring optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} -alkyl, dicyanovinyl,
15 cyano, nitro, and dinitrovinyl,
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

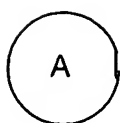
28. A method according to claim 27, wherein the compound is selected from
20 2-[[2-(4-chlorophenyl)-1H-indol-3-yl]methylene]malononitrile,
2-(4-chlorophenyl)-indole,
2,3-dimethyl-5-cyano-7-ethylindole, or
4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-1H-pyrrole-3-carbonitril.

25

29. A method according to claim 10, wherein the compound is of the general formula (I)



wherein



is an aryl, or heteroaryl,

- R^1 is halogen, $-\text{CHO}$, $-\text{CO}_2R^{32}$, $-\text{COR}^{32}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{33}$, $-\text{C}(R^{33})(R^{34})$, $-\text{SOR}^{32}$, $-\text{SO}_2R^{32}$ or aryl substituted with from one to five substituents selected from halogen, $-\text{CHO}$, $-\text{CO}_2R^{32}$, $-\text{COR}^{32}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{33}$, $-\text{CH}(R^{33})(R^{34})$, $-\text{SOR}^{32}$, $-\text{SO}_2R^{32}$, wherein

R^{32} is hydrogen, alkyl, aryl, or heteroaryl; and

R^{33} and R^{34} independently of each other are halogen, $-\text{CHO}$, $-\text{CO}_2R^{35}$, $-\text{COR}^{35}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SOR}^{35}$, $-\text{SO}_2R^{35}$, wherein

- R^{35} is hydrogen or alkyl;

and is attached on a carbon atom adjacent to the carbon atom to which the hydroxy group is attached;

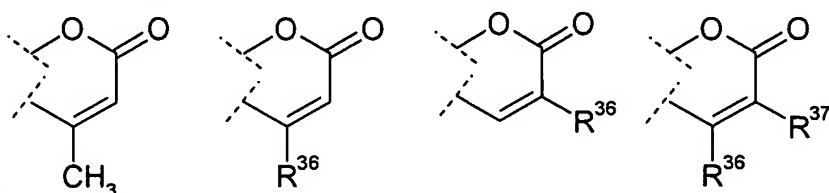
R^2 is $\text{C}(\text{X})_3$, NO_2 , alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl, wherein

X is halogen; and

- R^3 and R^4 independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

or

R^2 and R^3 together forms one of the diradicals



- wherein

R^{36} and R^{37} , independently of each other, are hydrogen, halogen, $\text{C}(\text{X})_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl, wherein

X is halogen;

and where the two connecting atoms are connected to adjacent carbon atoms; and

- R^4 is hydrogen, halogen, $\text{C}(\text{X})_3$, nitro, cyano, alkyl, alkyl-O-, alkyl-C(O)-, or aryl, or a pharmaceutically acceptable salt, solvate or prodrug thereof.

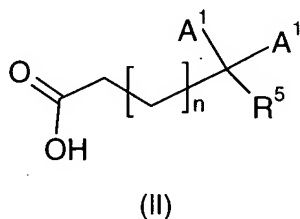
A method according to claim 29, wherein the compound is selected from

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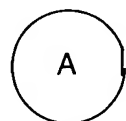
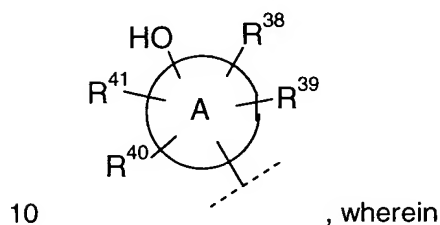
4-methoxy-2-nitrophenol,
 4-hydroxy-3-nitroacetophenone, or
 7-hydroxy-4-methyl-8-nitro-chromen-2-one.

5

31. A method according to claim 10, where the compound is of the general formula (II)



wherein A¹ is



is an aryl, or heteroaryl,

R³⁸ is halogen, -CHO, -CO₂R⁴², -COR⁴², -SO₃H, -CCl₃, -CF₃, -NO, -NO₂, -CN, -SOR⁴², or -SO₂R⁴², wherein

15 R⁴² is hydrogen or alkyl;

and is attached to a carbon atom adjacent to the carbon atom to which the hydroxy group is attached;

R³⁹, R⁴⁰, and R⁴¹ independently of each other are hydrogen, alkyl, nitro, cyano, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

20 R⁵ is hydrogen or alkyl; and

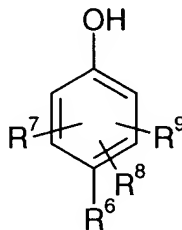
n is an integer of from 0 to 10

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

25 32. A method according to claim 31 wherein the compound is
 4,4-bis-(4-hydroxy-3-nitrophenyl)-valeric acid.

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33. A method according to claim 10 wherein the compound is of the general formula (III)



(III)

5 wherein

R^6 is halogen, $-\text{CHO}$, $-\text{CO}_2R^{43}$, $-\text{COR}^{43}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{44}$, $-\text{C}(R^{44})(R^{45})$, $-\text{SOR}^{43}$, $-\text{SO}_2R^{43}$ or aryl substituted with from one to five substituents selected from halogen, $-\text{CHO}$, $-\text{CO}_2R^{43}$, $-\text{COR}^{43}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CH}=\text{CH}-R^{44}$, $-\text{CH}(R^{44})(R^{45})$, $-\text{SOR}^{43}$, $-\text{SO}_2R^{43}$, wherein

10 R^{43} is hydrogen or alkyl; and

R^{44} and R^{45} independently of each other are halogen, $-\text{CHO}$, $-\text{CO}_2R^{46}$, $-\text{COR}^{46}$, $-\text{SO}_3\text{H}$, $-\text{CCl}_3$, $-\text{CF}_3$, $-\text{NO}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{SOR}^{46}$, $-\text{SO}_2R^{46}$, wherein

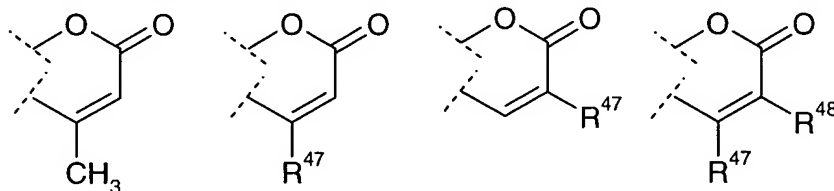
R^{46} is hydrogen, alkyl, or aryl;

R^7 is alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-; and

15 R^8 and R^9 independently of each other are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, alkyl-C(O)-O-, or aryl;

or

R^7 and R^8 together forms the diradical



20 wherein R^{47} and R^{48} , independently of each other, are hydrogen, alkyl, nitro, halogen, alkyl-O-, alkyl-C(O)-, or alkyl-C(O)-O-,

where the two valence atoms are connected to adjacent carbon atoms; and

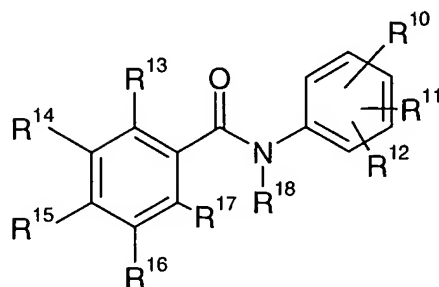
R^9 is hydrogen, alkyl, nitro, halogen, alkyl-O-, or alkyl-C(O)-

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

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34. A method according to claim 10, wherein the compound is of the general formula (IV)



(IV)

wherein

5 R¹⁰, R¹¹ and R¹² independently of each other are hydrogen, trifluoromethyl, nitro, cyano, alkyl-S-, R⁴⁹SO_y-, R⁴⁹-O-, N(R⁵⁰)(R⁵¹)-, alkyl, halogen, or aryl-S-, wherein y is an integer of 1 or 2;

R⁴⁹, R⁵⁰ and R⁵¹ independently of each other are hydrogen or alkyl;

wherein at least one of R¹⁰, R¹¹ and R¹² is different from hydrogen;

10 and

R¹³, R¹⁴, R¹⁵, R¹⁶ and R¹⁷ independently of each other are hydrogen, halogen, hydroxy, cyano, or alkyl, aryl, aryl-S-, or heteroaryl, optionally substituted with halogen;

or

15 R¹³ and R¹⁴ together form a conjugated alkenylene, which together with the benzene ring forms a fused aromatic ring system, which may optionally be substituted with one or more substituents selected from the group consisting of hydroxy, methyl, halogen, CF₃, alkyl-O-, nitro, and cyano; and

20 R¹⁵, R¹⁶ and R¹⁷, independently of each other, are hydrogen, halogen, hydroxy, halogen, or alkyl optionally substituted with halogen

or

25 R¹⁴ and R¹⁵ together form a conjugated alkenylene, which together with the benzene ring forms a fused aromatic ring system, which may optionally be substituted with one or more substituents selected from the group consisting of hydroxy, methyl, halogen, CF₃, alkyl-O-, nitro, and cyano; and

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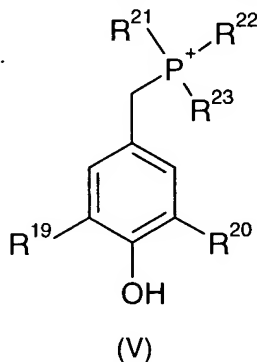
R^{13} , R^{16} and R^{17} independently of each other are hydrogen, halogen, hydroxy, halogen, or alkyl, aryl or heteroaryl, optionally substituted with halogen;

and

- 5 R^{18} is hydrogen;
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

35. A method according to claim 34, wherein the compound is selected from
10 tert-butyl-5-chloro-N-(2-chloro-4-nitrophenyl)-2-hydroxy-6-methylbenzamide,
N-1-[4-cyano-3-(trifluoromethyl)phenyl]-3,5-di(trifluoromethyl)benzamide,
N-(4-cyanophenyl)benzamide,
2'-chloro-1-hydroxy-4'-nitro-2-naphthanilide,
N-(2-chloro-4-bromophenyl)-5-bromosalicylanilide,
15 N-(2-chloro-4-nitrophenyl)-3-tert-butyl-6-methylsalicylanilide,
3,6-dinitrocarbazole, or
N-(3-cyano-4-phenylsulfanyl-phenyl)-3-trifluoromethyl-benzamide.

- 20 36. A method according to claim 10, wherein the compound is of the general formula (V)



wherein R^{19} and R^{20} independently of each other are alkyl;

and

- 25 R^{21} , R^{22} and R^{23} independently of each other are selected from alkyl, cycloalkyl, or aryl
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

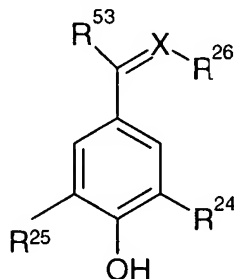
37. A method according to claim 36, wherein the compound is selected from

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(3,5-di-tert-butyl-4-hydroxybenzyl)triphenylphosphonium bromide,
 (3,5-di-tert-butyl-4-hydroxybenzyl)tricyclohexylphosphonium bromide,
 (3,5-di-tert-butyl-4-hydroxybenzyl)tributylphosphonium bromide, or
 (3,5-di-tert-butyl-4-hydroxybenzyl)trioctylphosphonium bromide.

5

38. A method according to claim 10, wherein the compound is of the general formula (VI)



10

(VI)

wherein

R^{24} and R^{25} independently of each other are alkyl or cycloalkyl;

and

$X = C(R^{52})-$; wherein

15

R^{52} is hydrogen, cyano, nitro, alkyl-S(O)₂-, tetrazole, alkyl-S-, alkyl-C(O)-, or alkyl-O-C(O)-, halogen, haloalkyl, (R⁵³)₂-N-C(O)-, -P(O)(O-R⁵³)₂, aryl, heteroaryl, wherein said aryl and heteroaryl are optionally substituted with one or more substituents selected from nitro, cyano, halogen, haloalkyl, -C(O)-R⁵³, -C(O)-O-R⁵³, -C(O)-N-(R⁵³)₂, -S(O)₂-O-R⁵³, -S(O)-R⁵³, -S(O)₂-R⁵³, -S(O)₂-N-(R⁵³)₂, or -O-R⁵³, wherein

20

R^{53} is hydrogen, or alkyl or phenyl optionally substituted with halogen; and

R^{26} is cyano, nitro, R⁵⁴-S(O)₂-, tetrazole, alkyl-C(O)-, or alkyl-O-C(O)-, haloalkyl, -S(O)-alkyl, -S(O)₂O-alkyl, -S(O)₂-N-(R⁵⁴)₂, -C(O)-N(R⁵⁴)₂, wherein

25

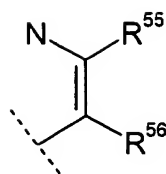
R^{54} is hydrogen, or alkyl or phenyl optionally substituted with halogen;

or

$X = N-$, and

R^{26} is cyano, nitro, R⁵⁴-S(O)₂-, alkyl-C(O)-, alkyl-O-C(O)-, or

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wherein

R^{54} is hydrogen, or alkyl or phenyl optionally substituted with halogen; and

R^{55} and R^{56} independently of each other are cyano, nitro, R^{57} -S(O)₂-, alkyl-C(O)-, or alkyl-O-C(O)-, wherein

R^{57} is hydrogen, or alkyl or phenyl optionally substituted with halogen;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

10

39. A method according to claim 38, wherein the compound is selected from

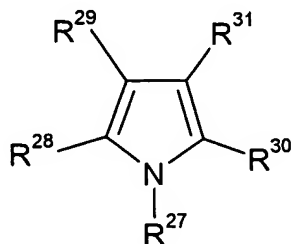
2-cyano-3-(3,5-di-tert-butyl-4-hydroxyphenyl)-acrylic acid ethyl ester,

2-(3,5-di-tert-butyl-4-hydroxy-benzylidene)-malonic acid diethyl ester,

2-amino-S-[(3,5-di-tert-butyl-4-hydroxybenzylidene)-amino]-but-2-enedinitrile, or

15 2-(3,5-di-tert-butyl-4-hydroxy-benzylidene)-indan-1,3-dione.

40. A method according to claim 10, wherein the compound is of the general formula (VII)



(VII)

20

wherein

R^{27} is hydrogen or alkyl-O-CH₂-;

R^{28} and R^{29} independently of each other are hydrogen, halogen, dicyanovinyl,

cyano, nitro, dinitrovinyl, alkyl optionally substituted with halogen, or aryl optionally

25 substituted with one or more substituents selected from the group consisting of halogen, dicyanovinyl, cyano, nitro, and dinitrovinyl,

or

R^{28} and R^{29} together forms a benzene ring optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} -alkyl, dicyanovinyl, cyano, nitro, and dinitrovinyl;

and

5 R^{30} is halogen, dicyanovinyl, cyano, nitro, dinitrovinyl, alkyl optionally substituted with halogen, or aryl optionally substituted with one or more substituents selected from the group consisting of halogen, dicyanovinyl, cyano, nitro, and dinitrovinyl; and R^{31} is hydrogen, halogen, dicyanovinyl, cyano, nitro, dinitrovinyl, alkyl optionally substituted with halogen, or aryl optionally substituted with one or more substituents
10 selected from the group consisting of halogen, dicyanovinyl, cyano, nitro, and dinitrovinyl;

or

R^{30} and R^{31} together forms a benzene ring optionally substituted with one or more substituents selected from the group consisting of halogen, C_{1-6} -alkyl, dicyanovinyl,
15 cyano, nitro, and dinitrovinyl,
or a pharmaceutically acceptable salt, solvate or prodrug thereof.

41. A method according to claim 40, wherein the compound is selected from
20 2-[[2-(4-chlorophenyl)-1H-indol-3-yl]methylene]malononitrile,
2-(4-chlorophenyl)-indole,
2,3-dimethyl-5-cyano-7-ethylindole, or
4-bromo-2-(4-chlorophenyl)-1-ethoxymethyl-5-trifluoromethyl-1H-pyrrole-3-carbonitril.

25 42. A method according to claim 10, wherein the compound is a chemical uncoupler as defined in Assay (II), as described in the specification.

43. A method according to claim 10, wherein the compound is a cation.
30